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(54) **DISPENSER AND APPARATUS AND METHOD FOR FILLING A DISPENSER**

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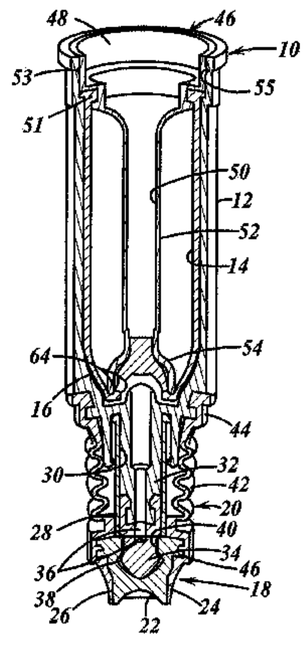
(57) **ABSTRACT**

A dispenser for holding multiple doses of fluids or other substances, and for dispensing the substances, has a vial, a flexible bladder received within the vial, and a variable volume storage chamber formed between the bladder and vial. A filling valve is coupled in fluid communication with the storage chamber and defines (1) a normally closed, fluid-tight position hermetically sealing the storage chamber from the ambient atmosphere, and (2) an open position allowing the passage of fluid through the valve both to evacuate the storage chamber and to introduce fluid through the valve to fill the storage chamber. A pump is coupled in fluid communication with the storage chamber for pumping fluids out of the storage chamber. A dispensing valve is coupled in fluid communication with the pump and defines (1) a normally closed, fluid-tight position preventing the passage of fluid out of the dispenser, and (2) an open position for dispensing pumped fluid therethrough. The sealed, empty dispenser is sterilized, such as by applying gamma radiation thereto. Then, the sterilized, sealed, empty dispenser is filled with fluid by engaging the filling valve with an evacuating/dispensing member to evacuate the storage chamber, and by introducing fluid from the filling member through the open filling valve and into the storage chamber. The filling member is withdrawn from the valve, and a spring moves the valve to a closed position to hermetically seal the fluid within the dispenser.

46 Claims, 9 Drawing Sheets



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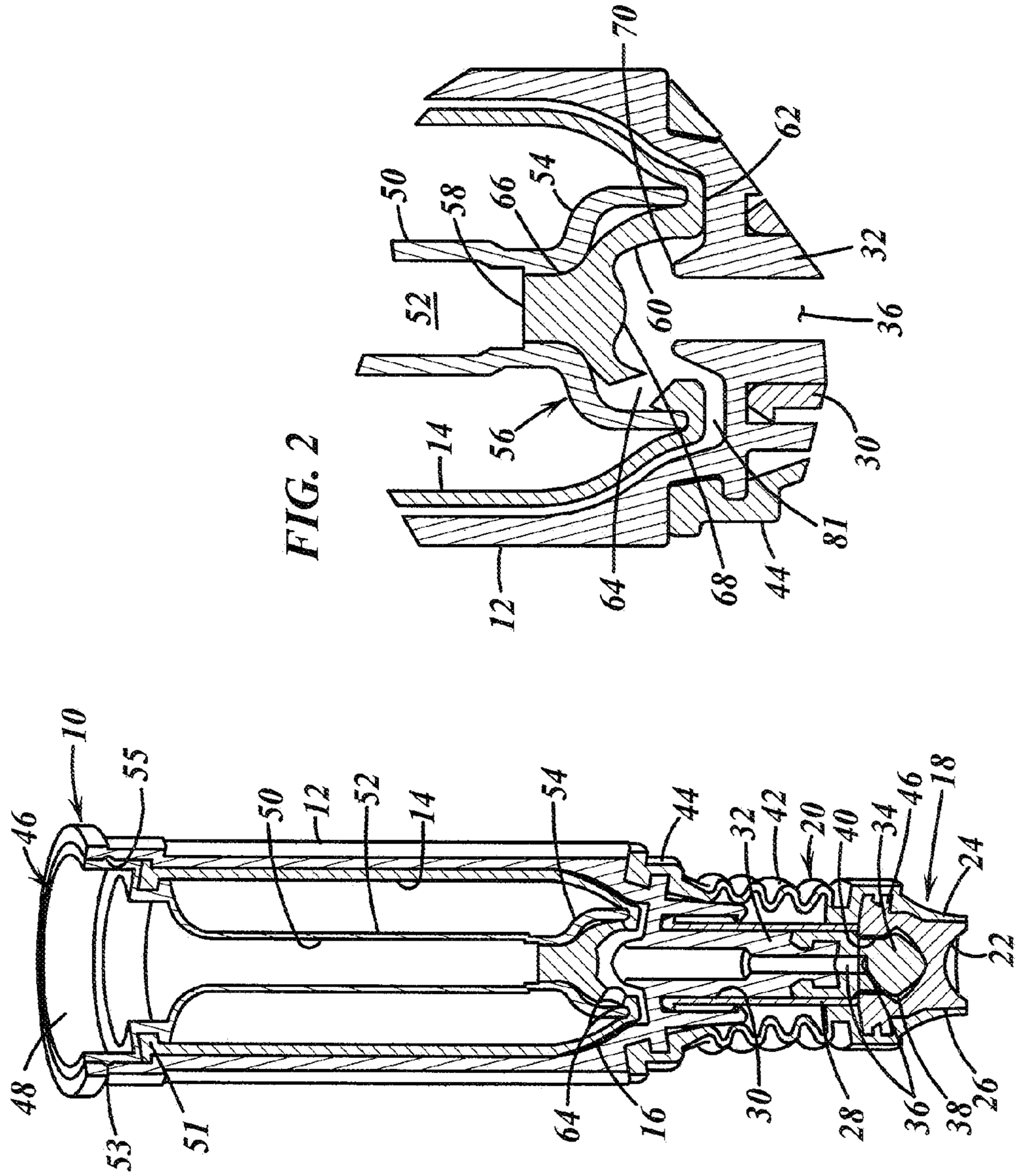
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FIG. 2

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FIG. 1

FIG. 3

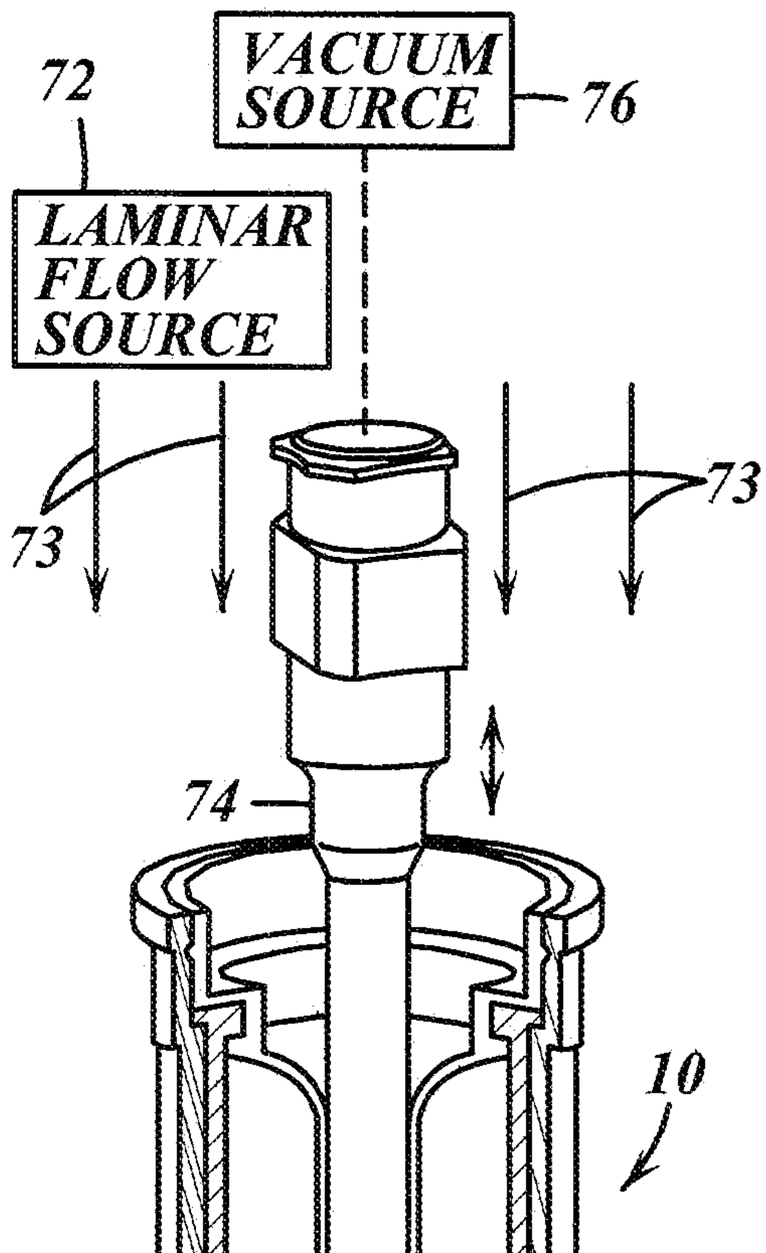
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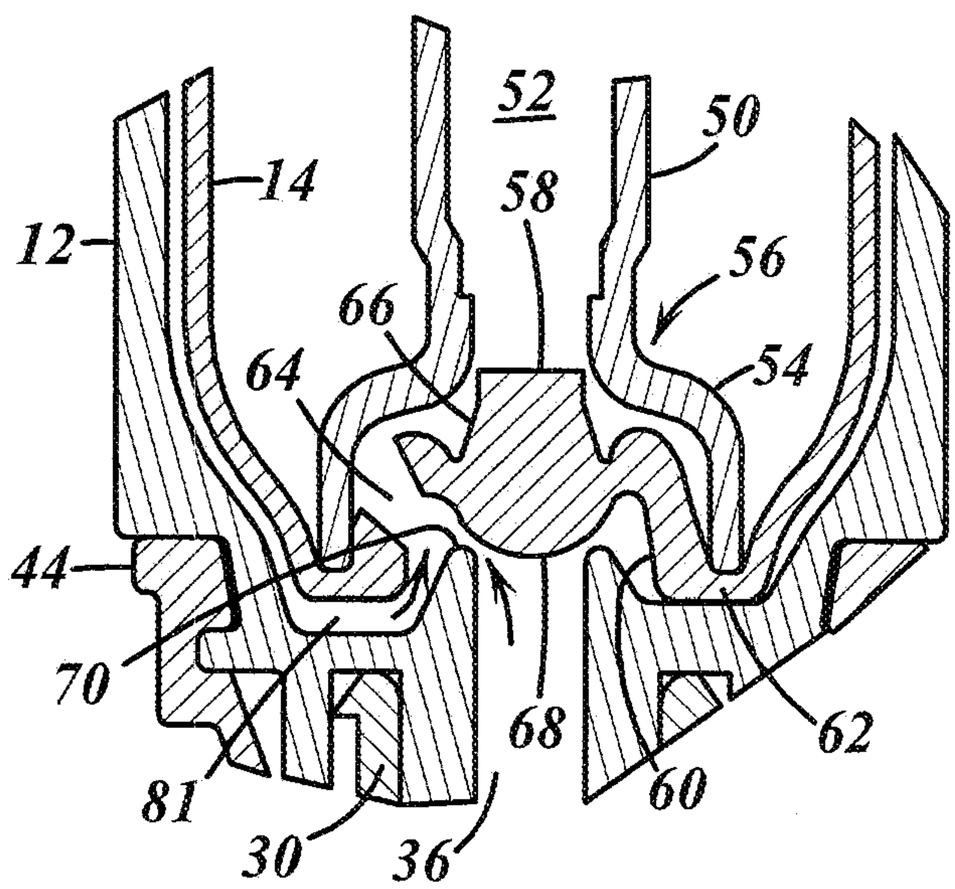
FIG. 4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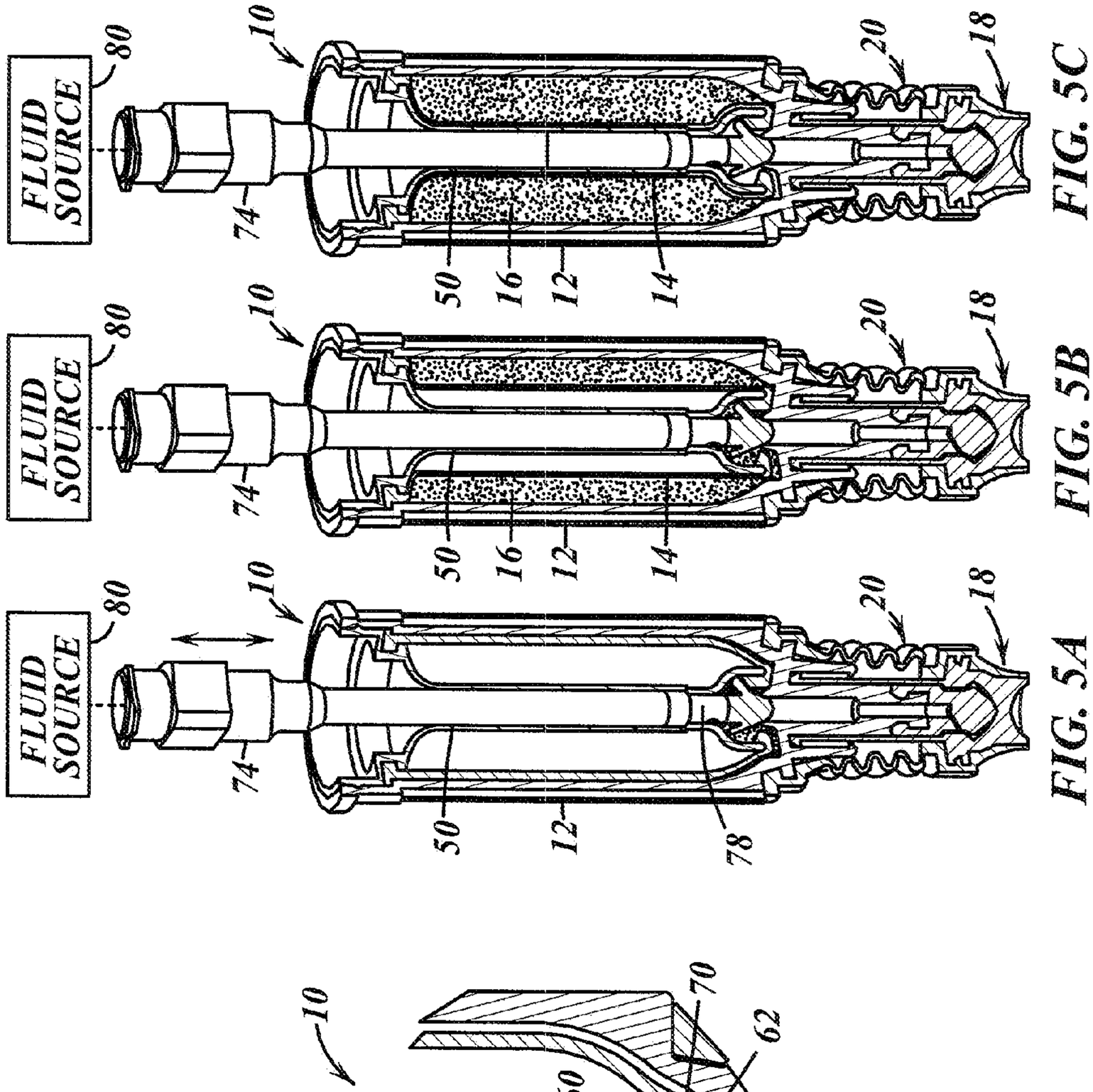

FIG. 5C

FIG. 5B

FIG. 5A

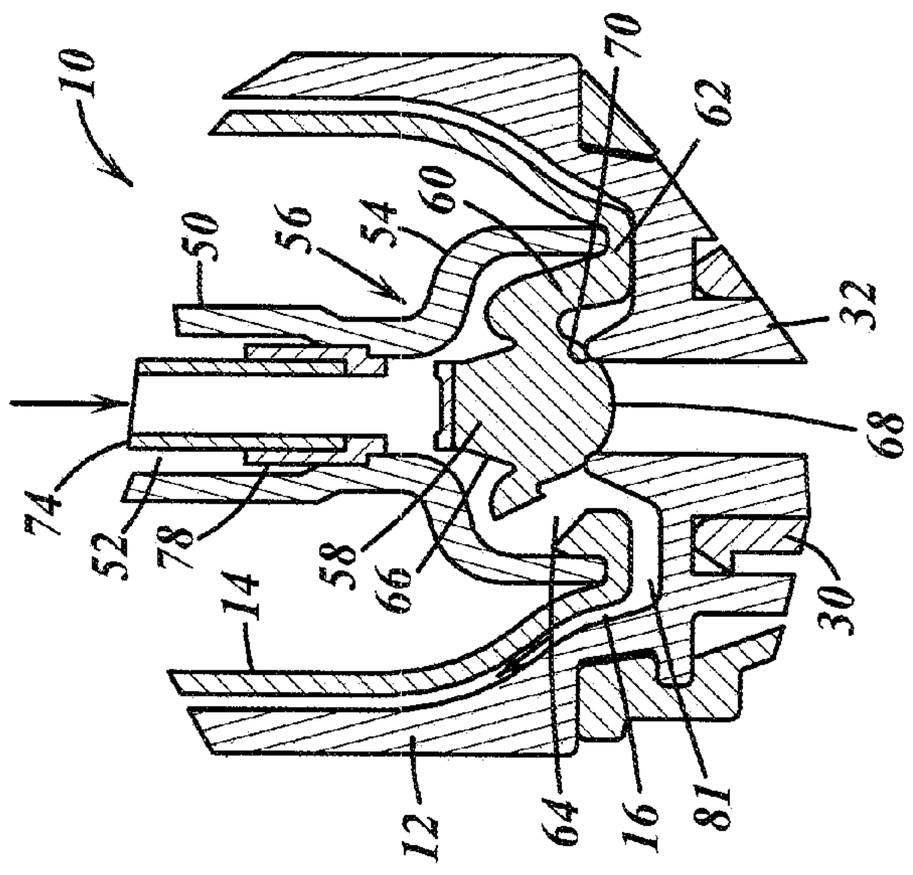

FIG. 5D

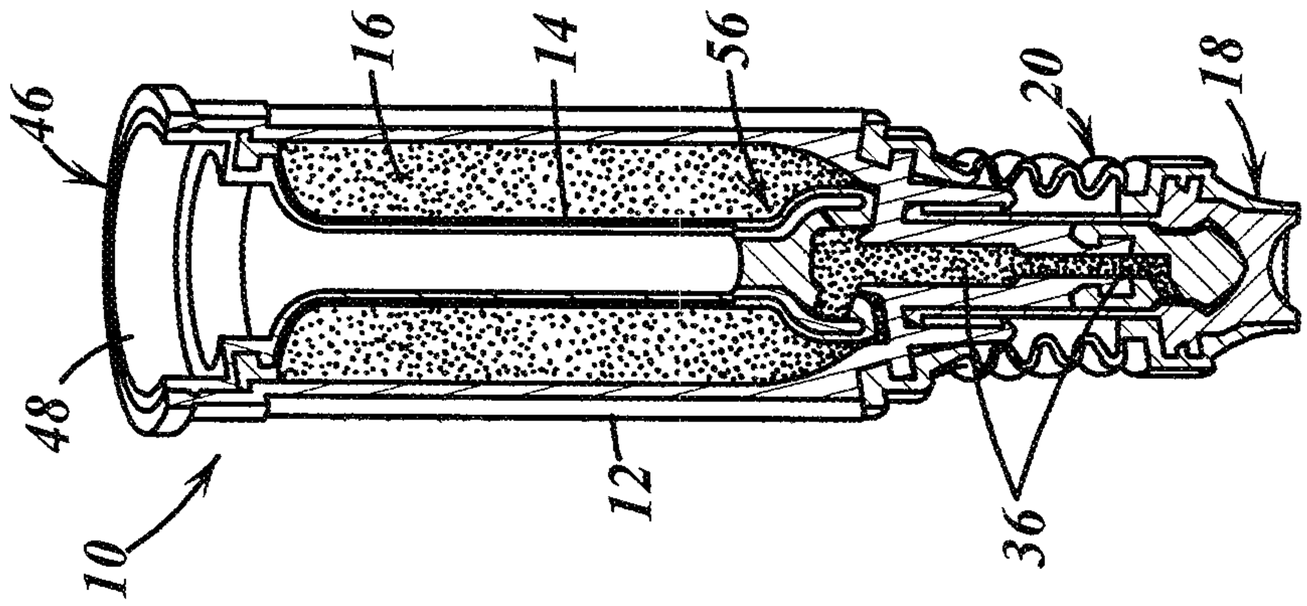
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FIG. 6A

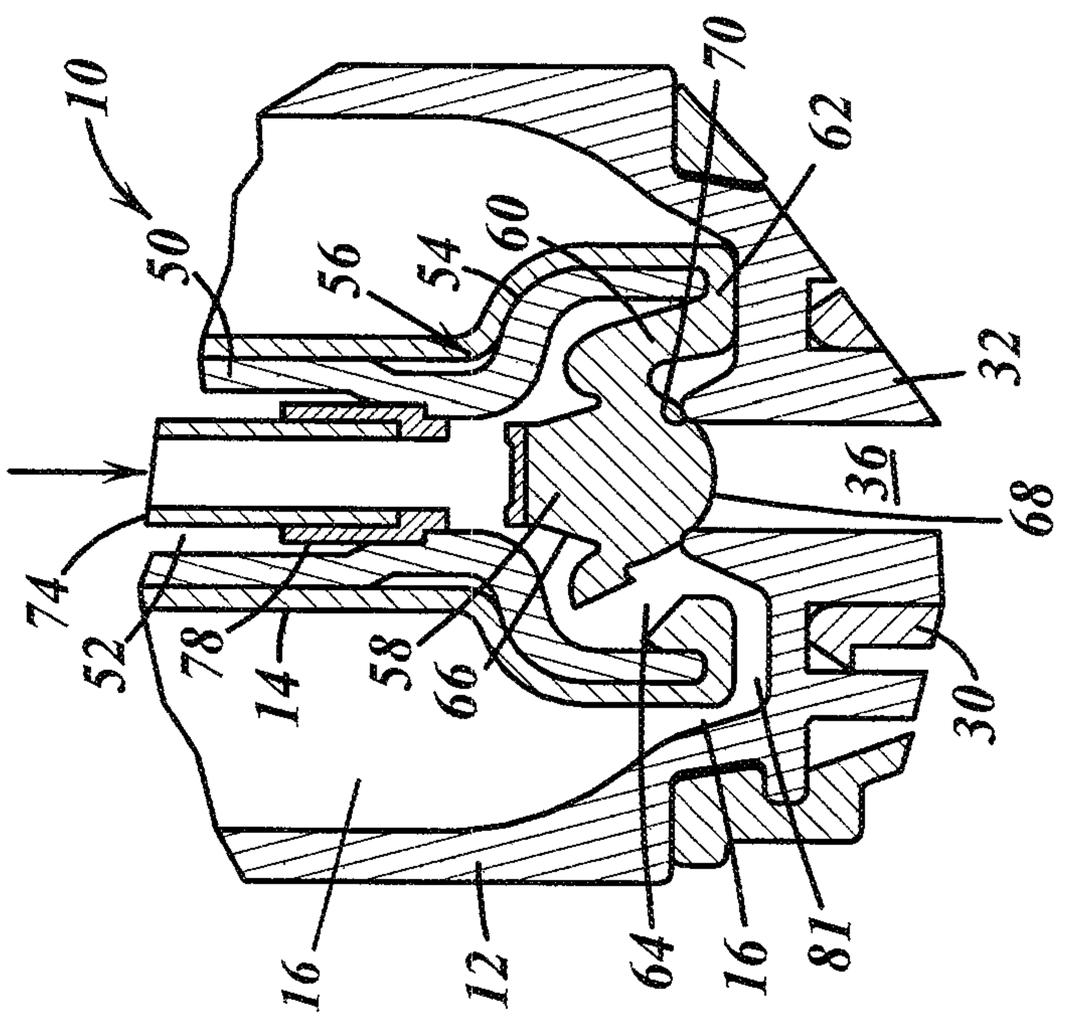
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FIG. 6B

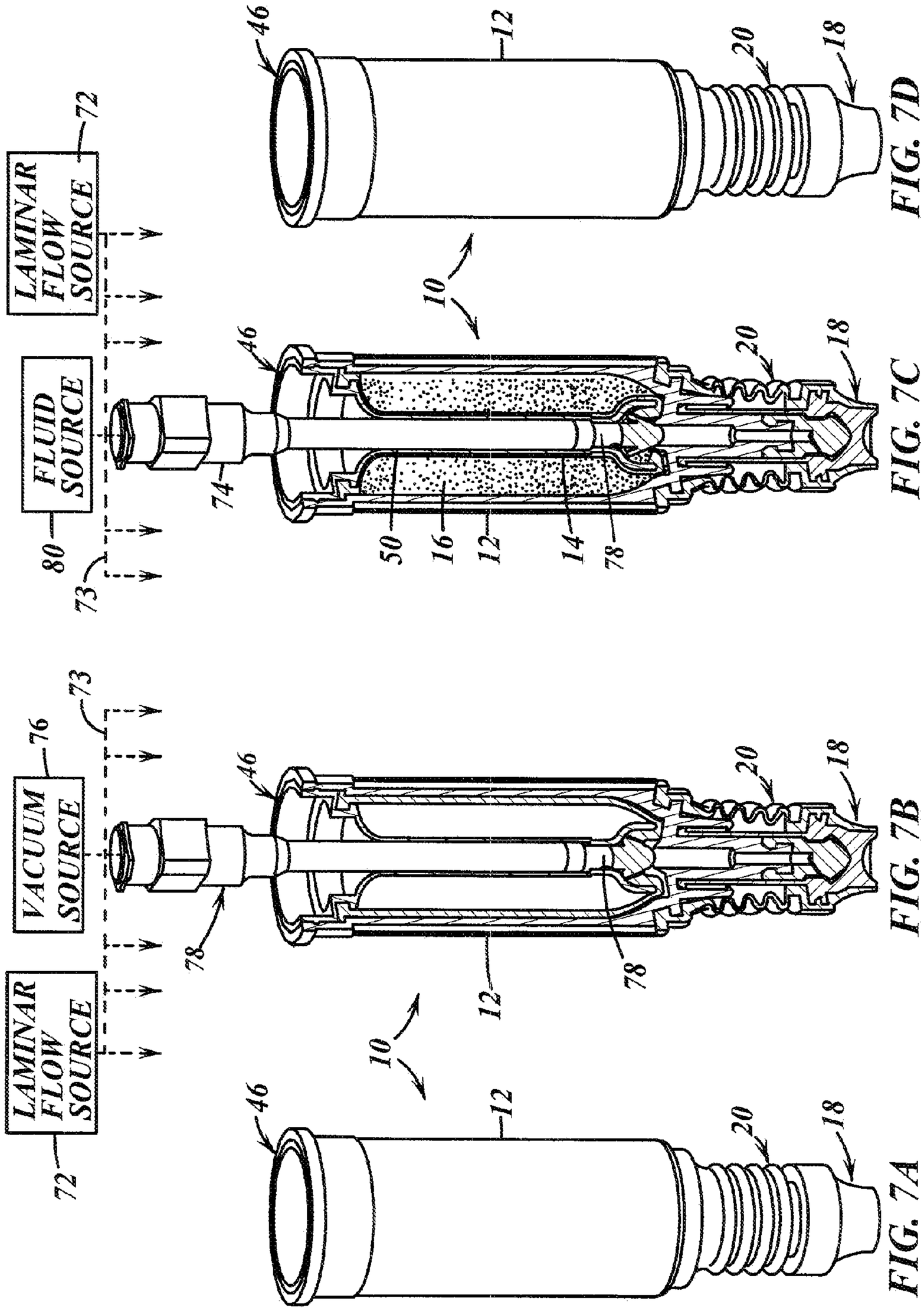

FIG. 7D

FIG. 7C

FIG. 7B

FIG. 7A

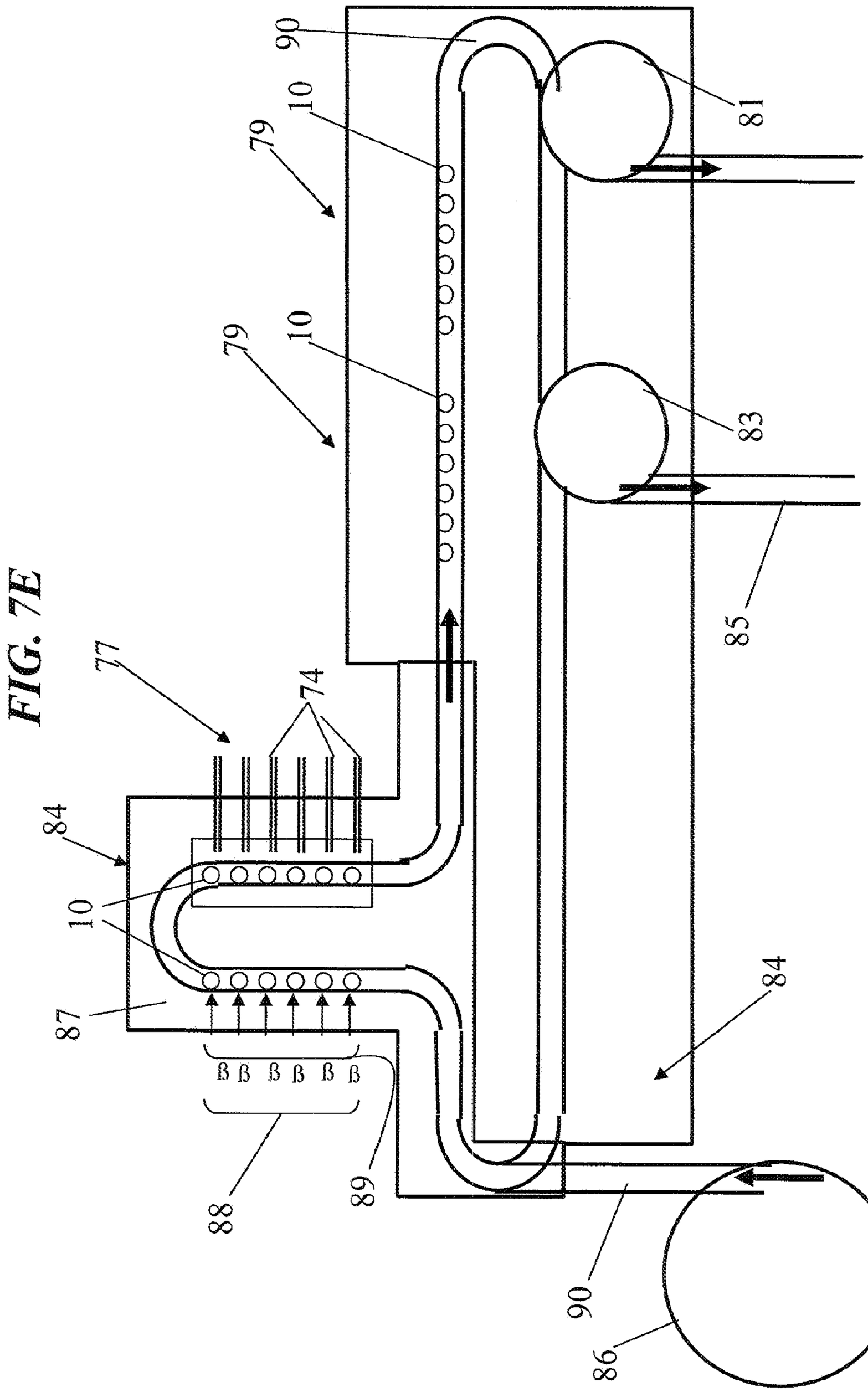

FIG. 7E

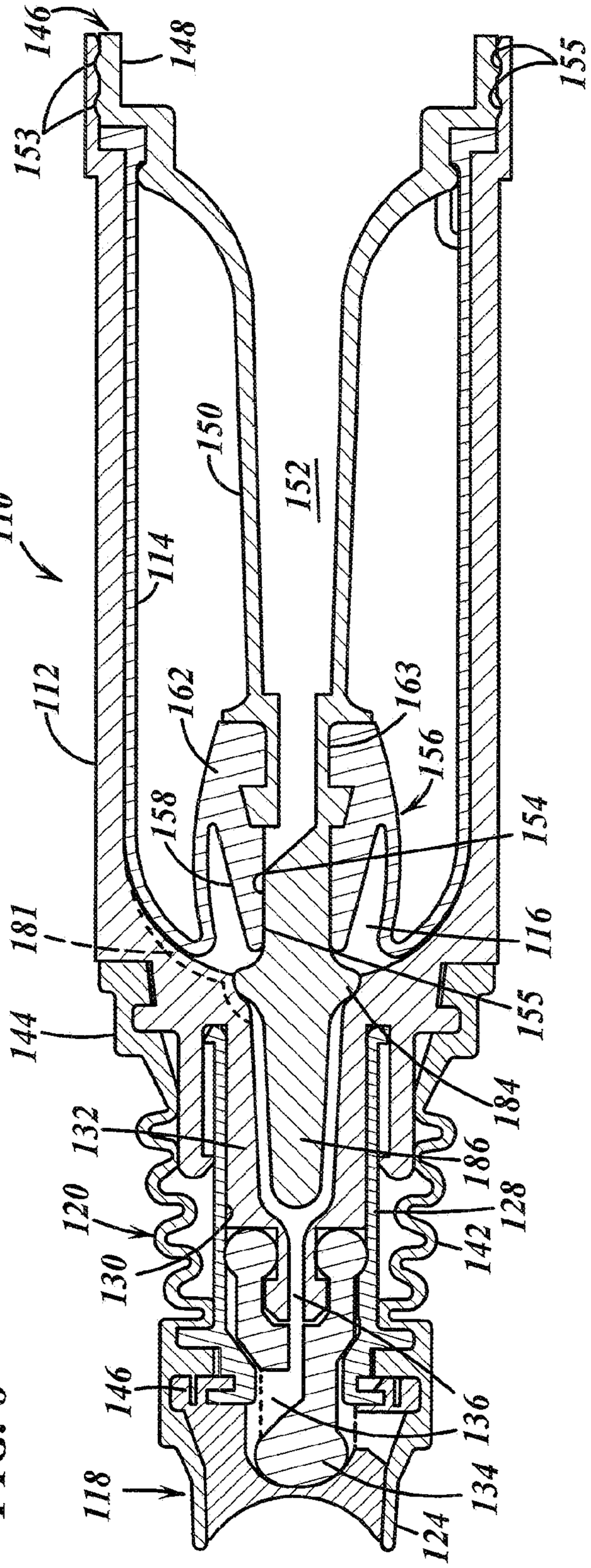
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FIG. 8

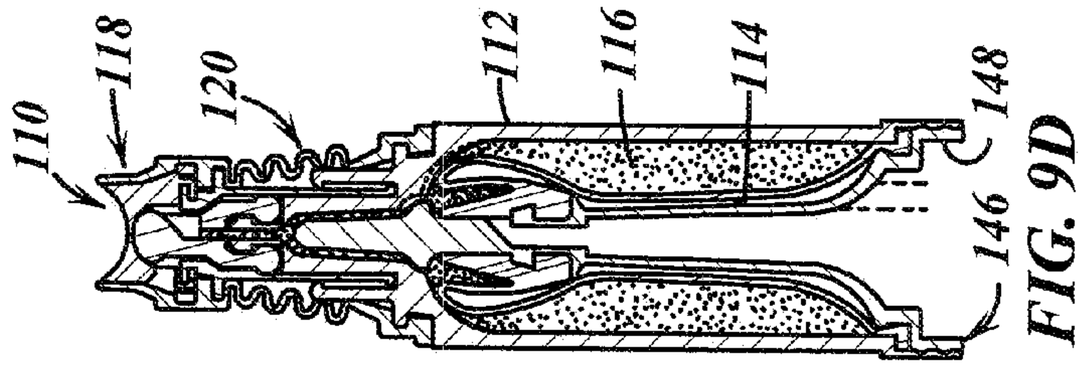

FIG. 9D

FIG. 9C

FIG. 9B

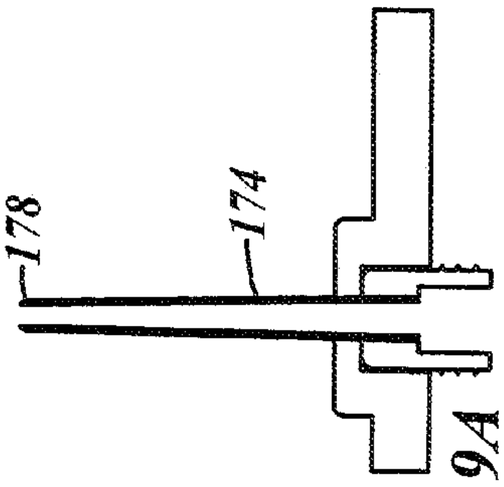

FIG. 9A

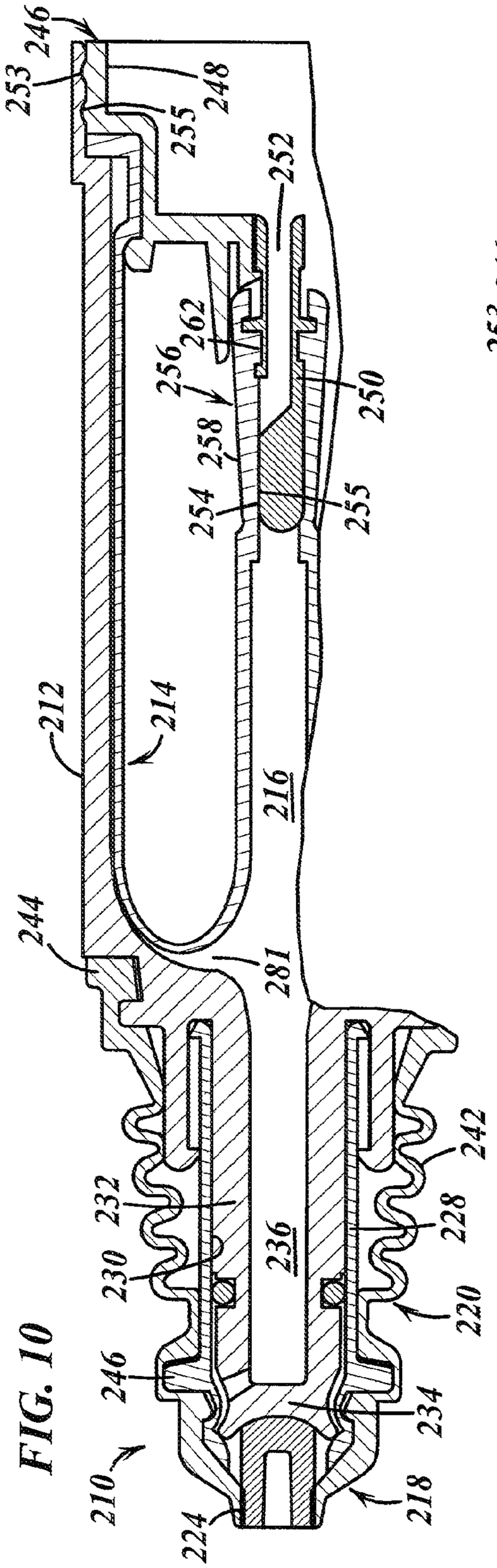
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FIG. 10

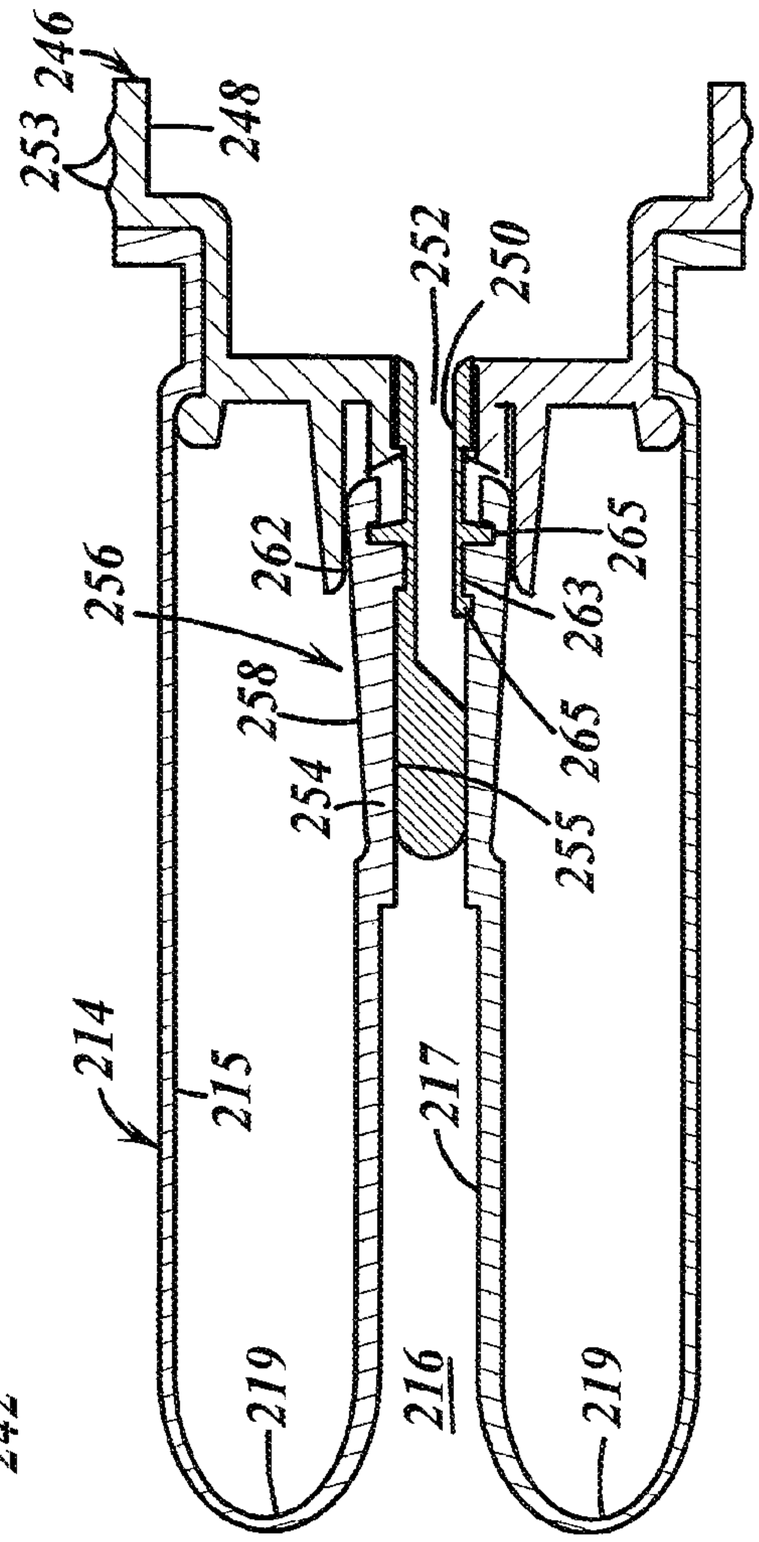
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FIG. 11

DISPENSER AND APPARATUS AND METHOD FOR FILLING A DISPENSER

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 12/984,482, entitled "Dispenser and Apparatus and Method for Filling a Dispenser," filed Jan. 4, 2011, now U.S. Pat. No. 8,627,861, which is a continuation of U.S. application Ser. No. 12/025,362, entitled "Dispenser and Apparatus and Method for Filling a Dispenser," filed Feb. 4, 2008, now U.S. Pat. No. 7,861,750, which is a continuation of U.S. application Ser. No. 11/349,873, entitled "Dispenser and Apparatus and Method for Filling a Dispenser," filed Feb. 8, 2006, now U.S. Pat. No. 7,328,729, which is a continuation of U.S. application Ser. No. 10/843,902, filed May 12, 2004, entitled "Dispenser and Apparatus and Method for Filling a Dispenser," now U.S. Pat. No. 6,997,219, which claims priority to similarly-titled U.S. Application No. 60/469,677, filed May 12, 2003; and to similarly-titled U.S. Application No. 60/471,592, filed May 19, 2003, and to U.S. Application No. 60/488,355, filed Jul. 17, 2003, titled "Piston-Type Dispenser with One-Way Valve for Storing and Dispensing Metered Amounts of Substances, and Pivoting Cover for Covering Dispensing Portion Thereof," and to U.S. Application No. 60/539,814, filed Jan. 27, 2004, entitled "Piston-Type Dispenser with One-Way Valve for Storing and Dispensing Metered Amounts of Substances," the disclosures of which are hereby expressly incorporated by reference as part of the present disclosure.

FIELD OF THE INVENTION

The present invention relates to dispensers for containing and dispensing fluids and other substances, such as medicaments, and more particularly, to dispensers for holding multiple doses of fluids and other substances, and to apparatus and methods for filling such dispensers with fluids and other substances.

BACKGROUND INFORMATION

A typical medicament dispenser includes a body defining a storage chamber, a fill opening in fluid communication with the body, and a stopper or cap for sealing the fill opening after filling the storage chamber to hermetically seal the medicament within the dispenser. In order to fill such prior art dispensers with a sterile fluid or other substance, such as a medicament, it is typically necessary to sterilize the unassembled components of the dispenser, such as by autoclaving the components and/or exposing the components to gamma radiation. The sterilized components then must be filled and assembled in an aseptic isolator of a sterile filling machine. In some cases, the sterilized components are contained within multiple sealed bags or other sterile enclosures for transportation to the sterile filling machine. In other cases, the sterilization equipment is located within the isolator of the sterile filling machine. In the isolator, the storage chamber is filled with the fluid or other substance, and then the sterilized stopper is assembled to the dispenser to plug the fill opening and hermetically seal the fluid or other substance in the dispenser.

One of the drawbacks of such prior art dispensers, and processes and equipment for filling such dispensers, is that the filling process is time consuming, and the processes and equipment are expensive. Further, the relatively complex

nature of the filling processes and equipment can lead to more defectively filled dispensers than otherwise desired.

The present inventor has recognized the advantages of sterilizing a sealed, empty dispenser, and then filling the sterilized, sealed, empty dispenser under a laminar flow to maintain aseptic conditions during filling. For example, U.S. Pat. No. 6,604,561, entitled "Medicament Vial Having a Heat-Sealable Cap, and Apparatus and Method for Filling the Vial", which is assigned to the Assignee of the present invention and is hereby expressly incorporated by reference as part of the present disclosure, discloses a vial including a resealable stopper. The resealable stopper is first sealed to the empty vial, and then the empty vial/stopper assembly is sterilized, such as by applying gamma radiation thereto. The sterilized, sealed, empty vial/stopper assembly is then filled by piercing the resealable stopper with a needle, and introducing the fluid or other substance through the needle and into the chamber of the vial. Then, the needle is withdrawn, and laser radiation is transmitted onto the penetrated region of the stopper to seal the needle hole and hermetically seal the sterile fluid or other substance within the vial/stopper assembly.

Although this resealable stopper, apparatus and method overcome many of the drawbacks and disadvantages associated with prior art equipment and processes for sterile filling, in certain instances it may not be desirable to employ a resealable stopper, a needle for piercing the stopper, and/or a laser for resealing the penetrated region of a stopper.

Accordingly, it is an object of the present invention to overcome one or more of the above-described drawbacks and/or disadvantages, and to provide a dispenser, and an apparatus and method for filling the dispenser, wherein the dispenser may be sealed and sterilized in an empty condition, and the sterilized, sealed, empty dispenser may be filled without disassembling the dispenser to hermetically seal the sterilized fluid or other substance within the dispenser.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a perspective cross-sectional view of a dispenser;

FIG. **2** is a partial, cross-sectional view of the dispenser of FIG. **1** showing the filling valve for evacuating the interior of the dispenser and for introducing a fluid or other substance into the storage chamber of the dispenser to fill the dispenser;

FIG. **3** is a partial, cross-sectional view of the dispenser of FIG. **1** showing a filling/evacuating member received within the fill tube of the dispenser and engaging the flexible valve member of the filling valve for opening the filling valve;

FIG. **4** is a partial, cross-sectional view of the dispenser of FIG. **1** showing the filling valve in an open condition such that the flexible valve member is located in a mid-position for evacuating air or other gases from the interior of the dispenser prior to filling same with a fluid or other substance, such as a medicament;

FIG. **5**A is a perspective, cross-sectional view of the dispenser of FIG. **1** showing a filling member received within the fill tube of the dispenser and engaging the flexible valve member to fully open the valve member and, in turn, introduce a fluid or other substance, such as a medicament, through the open valve and into the storage chamber.

FIG. **5**B is a perspective, cross-sectional view of the dispenser of FIG. **5**A showing the storage chamber about half filled with a fluid or other substance, and showing the flexible bladder in a correspondingly partially collapsed condition.

FIG. **5**C is a perspective, cross-sectional view of the dispenser of FIG. **5**A showing the storage chamber filled with a fluid or other substance, and showing the flexible bladder in a correspondingly fully collapsed condition.

FIG. **5**D is a partial, cross-sectional view of the dispenser of FIG. **1** showing the filling member engaging the flexible valve member in the fully open position and the flow path of a fluid or other substance through the open filling valve, through one or more grooves formed at the base of the flexible bladder between the bladder and vial base, and into the storage chamber to fill the storage chamber;

FIG. **6**A is a perspective, cross-sectional view of the dispenser of FIG. **1** showing the storage chamber filled with a fluid or other substance, and the pump primed with such fluid or other substance.

FIG. **6**B is a partial, cross-sectional view of the dispenser of FIG. **1** showing the filling member engaging the flexible valve member in the fully open position and the storage chamber in the filled condition;

FIG. **7**A is a perspective view of the dispenser of FIG. **1** in an empty, sealed, sterilized condition prior to introducing the dispenser into a sterile filling machine for filling the dispenser;

FIG. **7**B is a perspective, cross-sectional view of the dispenser of FIG. **1** located in a vacuum station of a sterile filling machine and illustrating a filling/evacuating member received within the fill tube of the dispenser for evacuating the interior of the dispenser;

FIG. **7**C is a perspective, cross-sectional view of the dispenser of FIG. **1** located in a filling station of a sterile filling machine, and illustrating a filling member received within the fill tube of the dispenser with the storage chamber in the filled condition and the flexible bladder in a correspondingly collapsed condition;

FIG. **7**D is a perspective view of the dispenser of FIG. **1** showing the dispenser in an Intact™ condition wherein the dispenser is filled, sealed, sterilized and ready for discharge from the sterile filling machine;

FIG. **7**E is a somewhat schematic, top plan view of a sterile filling machine for use in filling dispensers;

FIG. **8** is a cross-sectional view of another dispenser including a different type of filling valve;

FIG. **9**A is cross-sectional view of the dispenser of FIG. **8** being loaded into the filling station of a sterile filling machine;

FIG. **9**B is a cross-sectional view of the dispenser of FIG. **8** in the filling station of a sterile filling machine;

FIG. **9**C is a cross-sectional view of the dispenser of FIG. **8** being filled in the filling station of a sterile filling machine;

FIG. **9**D is a cross-sectional view of the dispenser of FIG. **8** after filling in the sterile filling machine and ready for use;

FIG. **10** is a partial, cross-sectional view of another dispenser including a different type of filling valve; and

FIG. **11** is cross-sectional view of the flexible bladder of the dispenser of FIG. **10**.

SUMMARY OF THE INVENTION

In one embodiment, a dispenser comprises a body; a variable-volume storage chamber formed within the body; and a filling valve coupled in fluid communication with the storage chamber. The filling valve defines (1) a normally closed, fluid-tight position hermetically sealing the storage chamber from the ambient atmosphere, and (2) an open position allowing the passage of fluid through the valve to withdraw fluid therethrough to evacuate the storage chamber and/or to introduce fluid therethrough to fill the storage chamber. A pump is coupled in fluid communication with the storage chamber for pumping fluid out of the storage chamber; and a dispensing valve is coupled in fluid communication with the pump and defines (1) a normally closed, fluid-tight position preventing the passage of fluid therethrough, and (2) an open position for dispensing pumped fluid therethrough.

In one embodiment, the filling valve includes a flexible valve member, and a valve seat engagable with the flexible valve member. The flexible valve member is movable into the closed position in engagement with the valve seat to form a fluid-tight seal therebetween, and is movable into the open position spaced away from the valve seat to form a valve opening for the passage of fluid therebetween. The filling valve also may include a spring that urges the valve member toward the closed position. In one embodiment, the spring is formed integral with the flexible valve member. Also in an embodiment, the spring is approximately dome-shaped and applies both radially directed and axially directed forces to the flexible valve member to urge the valve member toward the closed position. At least one flow aperture is formed through the spring and is coupled in fluid communication between an inlet to the filling valve and the storage chamber.

Also in an embodiment, the filling valve includes a first valve seat and a first sealing surface movable relative to the first valve seat between the closed and open positions. The first sealing surface is engagable with the first valve seat in the closed position to form a fluid-tight seal therebetween, and is spaced away from the first valve seat in the open position to form a valve opening for the passage of fluid therethrough.

Also in an embodiment, the filling valve includes a second sealing surface and a second valve seat formed between the storage chamber and the dispensing valve. The second sealing surface is movable between an open position spaced away from the second valve seat for allowing the flow of fluid therethrough, and a closed position engagable with the second valve seat and forming a fluid-tight seal therebetween. The filling valve may include a flexible valve member defining the first sealing surface on one side thereof and the second sealing surface on another side thereof.

Another embodiment is directed to an apparatus for sterile filling a dispenser. In one embodiment, the dispenser includes a fill tube coupled in fluid communication with the filling valve. The apparatus for sterile filling includes at least one probe or filling member connectable in fluid communication with the filling valve to open the valve and withdraw fluid from the dispenser through the filling valve to evacuate the dispenser, and/or to introduce fluid from the probe and into the storage chamber of the dispenser.

The sterile filling apparatus may further comprise a vacuum source that is connectable in fluid communication with the probe for drawing a vacuum through the probe and, in turn, through a dispenser coupled in fluid communication with the probe, or that is otherwise connectable in fluid communication with the interiors of the dispensers, such as through the dispensing valves. The sterile filling apparatus also comprises a fluid source coupled in fluid communication with at least one probe for introducing fluid therethrough and into the storage chamber of a dispenser coupled in fluid communication with the probe. The sterile filling apparatus may further comprise a laminar flow source for introducing a substantially laminar flow of fluid over the at least one probe and dispenser coupled in fluid communication therewith.

Embodiments are also directed to a method for filling a dispenser, wherein the dispenser includes a body; a variable-volume storage chamber formed within the body; a filling valve coupled in fluid communication with the storage chamber and defining (1) a normally closed, fluid-tight position hermetically sealing the storage chamber from the ambient atmosphere, and (2) an open position allowing the passage of fluid through the valve to withdraw fluid therethrough to evacuate the storage chamber, and/or to introduce fluid therethrough to fill the storage chamber; a pump coupled in fluid communication with the storage chamber for pumping fluid out of the storage chamber; and a dispensing valve coupled in fluid communication with the pump and defining (1) a normally closed, fluid-tight position preventing the passage of fluid therethrough, and (2) an open position for dispensing pumped fluid therethrough. The method comprises the following steps:

(i) providing a filling probe or member coupled in fluid communication with a fluid source;

(ii) connecting the filling probe in fluid communication with the filling valve and, in turn, moving the filling valve from the closed to the open position;

(iii) introducing a fluid from the probe through the open filling valve and into the storage chamber; and

(iv) withdrawing the probe from the filling valve and, in turn, moving the filling valve from the open to the closed position and hermetically sealing the fluid within the storage chamber.

In one embodiment, the method further comprises the step of evacuating the interior of the dispenser prior to filling. In one such embodiment, the method further comprises the steps of:

connecting a probe coupled in fluid communication with a vacuum source in fluid communication with the filling valve and, in turn, moving the filling valve from the closed to the open position;

drawing a vacuum through the probe and, in turn, evacuating the storage chamber of the dispenser;

providing a substantially laminar flow of fluid over the probe and dispenser coupled in fluid communication therewith; and

sealing the pump and dispensing valve from the storage chamber during filling of the storage chamber to prevent a flow of fluid through the dispensing valve during filling of the storage chamber.

In another embodiment, the interior of the dispenser is evacuated by connecting a vacuum source in fluid communication with the interior of the dispenser through the dispensing valve. Then, after evacuating the dispenser, filling the variable-volume storage chamber through the filling valve.

One advantage of the present invention is that the dispenser may be assembled, sealed and sterilized empty. Then, the sterilized dispenser may be filled with a sterile fluid or other substance through the filling valve and without disassembling the dispenser.

Other advantages of the present invention will become more readily apparent in view of the following detailed description of embodiments and accompanying drawings.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

In FIG. **1**, a dispenser is indicated generally by the reference numeral **10**. The dispenser **10** comprises a rigid vial or body **12**, a flexible bladder **14** mounted within the rigid vial **12**, and a variable-volume storage chamber **16** formed between the vial and bladder for receiving therein a fluid or other substance, such as a medicament. The dispenser **10** further comprises a dispensing nozzle **18** and a pump **20** coupled in fluid communication between the dispensing nozzle **18** and the storage chamber **16** for pumping metered doses of the fluid or other substance from the storage chamber **16** through the dispensing nozzle.

The dispensing nozzle **18** includes a relatively rigid valve seat **22** and a flexible valve cover **24** mounted over the valve seat and defining an axially elongated, annular seam **26** therebetween. As described further below, the pump **20** forces a metered dose of fluid or other substance at sufficient pressure to open the valve (the "valve opening pressure") and force the fluid through the valve seam **26** and out of the dispenser. The valve cover **24** may form an interference fit with the valve seat **22** to thereby form a fluid-tight seal in the normally closed position and, in turn, maintain the fluid or other substance within the dispenser in a sterile and hermetically sealed condition. Further, as shown typically in FIG. **1**, the valve cover **24** defines a substantially tapered cross-sectional shape moving in the axial direction from the interior toward the exterior of the valve. This configuration requires progressively less energy to open each respective annular portion of the valve when moving axially from the interior toward the exterior of the valve. As a result, once the base of the valve is opened, the pressure is sufficient to cause the respective axial segments of the valve cover **24** to progressively open and then close after passage of fluid therethrough when moving in the axial direction to dispense a metered dose. Also, in some embodiments, during dispensing of a metered dose, a substantially annular segment of the valve cover **24** substantially always engages the valve seat **22** to maintain the fluid-tight seal across the valve **20** and thereby prevent ingress through the valve of germs, bacteria or other unwanted substances into the storage chamber.

The valve cover **24** and the valve seat **22** may take any of numerous different shapes and/or configurations that are currently known, or that later become known, such as any of the shapes and/or configurations disclosed in the following co-pending patent applications that are assigned to the Assignee of the present invention and are hereby expressly incorporated by reference as part of the present disclosure: U.S. Provisional application Ser. No. 10/640,500, filed Aug. 13, 2003, entitled "Container and Valve Assembly for Storing and Dispensing Substances"; U.S. Provisional Application No. 60/528,429, filed Dec. 10, 2003, entitled "Valve Assembly and Tube Kit for Storing and Dispensing Substances"; and U.S. Provisional Application No. 60/539,602, filed Jan. 27, 2003, entitled "Tubular Container and One-Way Valve Assembly for Storing and Dispensing Substances".

The pump **20** includes a rigid slide **28** defining therein an axially elongated bore **30**. A piston **32** is slidably received within the bore **30** and includes a piston tip **34** on the free end thereof. The piston **32** and tip **34** define a fluid conduit **36** extending therethrough. A dosage chamber **38** is formed between the piston tip **34** and an interior surface of the valve seat **22**. The fluid conduit **36** is coupled in fluid communication between the dosage chamber **38** and storage chamber **16** for dispensing fluid from the storage chamber into the dosage chamber upon actuation of the pump.

The slide **28** defines a reduced cross-sectional portion **40** that cooperates with the piston tip **34** to define the volume of the dosage chamber **38** and thus the dosage volume of the dispenser. The axial extent of the reduced portion **40** defines a compression zone within which the fluid or other sub-

stance is compressed by the piston and, in turn, forced through the dispensing nozzle **18**. On the downward stroke of the piston **32**, and prior to the piston tip **34** slidably engaging the reduced portion **40**, fluid is permitted to flow both forwardly in front of the piston, and rearwardly back over the sides of the piston tip. Then, when the piston tip **34** slidably engages the reduced portion **40**, a fluid-tight seal is formed therebetween, thus trapping a precise volume of fluid within the compression zone and forcing the precise volume of fluid through the valve. The valve seat **24** defines one or more apertures (not shown) extending between the dosage chamber and the seam **26** to allow the fluid to flow therethrough and out of the valve. The valve tip **34** may be made of an elastomeric material that is relatively soft in comparison to the slide **28** and reduced portion **40** thereof. For example, the valve tip **34** may be made of a polymeric material, such as the material sold under the trademark Kraton™, or a vulcanized rubber or other polymeric material. As may be recognized by those of ordinary skill in the pertinent art based on the teachings herein, these materials are only exemplary, however, and numerous other materials that are currently or later become known for performing the function of the valve tip equally may be used.

A spring portion or bellows **42** is formed integral with the valve cover **24** and extends between the base of the valve cover and the vial **12**. As can be seen, the piston **32** is formed integral with the vial **12** and extends axially therefrom. The spring **42** is fixedly secured at one end to the vial **12** at a first annular flange **44**, and is fixedly secured at another end to a second annular flange **46** extending outwardly from the base of the valve seat **22**. The pump **20** is actuated by moving at least one of the piston **32** and slide **30** relative to the other to cause the piston tip **34** to move axially within the slide to load the dosage chamber **38** and, in turn, dispense the metered dose of fluid or other substance from the dosage chamber and through the valve.

As may be recognized by those of ordinary skill in the pertinent art based on the teachings herein, the construction of many aspects of the dispenser **10**, including aspects of the vial, variable-volume storage chamber, pump and nozzle, may be the same as or similar to that described in any of co-pending U.S. patent application Ser. No. 10/001,745, filed Oct. 23, 2001, entitled "Fluid Dispenser Having A Rigid Vial And Flexible Inner Bladder", similarly titled U.S. patent application Ser. No. 10/691,270, filed Oct. 21, 2003, U.S. Provisional Application No. 60/519,961, filed Nov. 14, 2003, entitled "Delivery Device And Method Of Delivery", and U.S. Provisional Application No. 60/539,814, filed Jan. 27, 2004, entitled "Piston-Type Dispenser With One-Way Valve For Storing And Dispensing Metered Amounts Of Substances", each of which is assigned to the Assignee of the present invention, and is hereby expressly incorporated by reference as part of the present disclosure. In addition, the dispenser **10** may be mounted within any of the cartridges and/or housings shown in U.S. Patent Application No. 60/420,334, filed Oct. 21, 2002, entitled "Dispenser", and/or U.S. Patent Application No. 60/443,524, filed Jan. 28, 2003, entitled "Dispenser", each of which is assigned to the Assignee of the present invention, and is hereby expressly incorporated by reference as part of the present disclosure.

The dispenser **10** further comprises an end cap **46** including a mounting flange **48** that is received within the open end of the vial **12** and fixedly secured thereto, a filling tube **50** extending axially inwardly from the flange **48** and defining a fluid conduit **52** therein, and a substantially dome-shaped valve seat **54** formed at the other end of the filling tube and engaging the base of the bladder **14**. The flexible bladder **14** defines an annular sealing flange **51** that is compressed between the flange **48** of the end cap **46** and the vial **12** to form a fluid-tight seal therebetween. The flange **48** of the cap **46** defines a peripheral lobe **53** that is snap-fit into a corresponding annular recess **55** of the vial to fixedly secure the cap to the vial with the sealing flange **51** of the bladder compressed therebetween.

As shown in FIG. **2**, the bladder **14** and dome-shaped valve seat **54** cooperate to form a second or filling valve **56**. The filling valve **56** includes a valve member **58** formed integral with the bladder **14**, and a substantially dome-shaped spring portion **60** also formed integral with the bladder **14** and extending between the valve member **58** and a base portion **62** of the bladder. At least one valve aperture **64** is formed through the dome-shaped valve spring **60** to permit the flow of fluid and/or other substance therethrough when the filling valve is in the open position. The flexible valve member **58** defines a first sealing surface **66** that sealingly engages the valve seat **54** in the normally-closed position to form a fluid-tight seal therebetween. The spring **60** normally urges the valve member **58** axially upwardly in the Figure to cause the first sealing surface **66** to sealingly engage the valve seat and form a fluid-tight seal therebetween. As described further below, the spring **60** allows the flexible valve member **58** to be moved axially inwardly (or downwardly in the Figure) to, in turn, open the valve and allow the flow of fluid or other substance therethrough. The valve member **58** defines on its interior side a second sealing surface **68**, and the vial **12** defines at the inlet to the fluid conduit **36** a corresponding annular valve seat **70**. As described further below, in the open position of the filling valve **56**, the second sealing surface **68** may be moved into engagement with the valve seat **70** to form a fluid-tight seal therebetween to, in turn, prevent the flow of fluid into the fluid conduit **36** of the piston.

As may be recognized by those of ordinary skill in the pertinent art based on the teachings herein, the spring **60** of the filling valve **56** may take any of numerous different shapes and/or configurations, or may be formed of any of numerous different materials, that are currently, or later become known for performing the function of the spring as described herein. For example, the spring may define a shape other than a dome shape, or may not be formed integral with the bladder or the valve member. Also, the shape and/or material of construction of the spring may be selected to control the spring force applied to the valve member. One advantage of the substantially dome-shaped configuration, however, is that the dome shape imparts lateral (or radial) and axial forces to the flexible valve member **58** to facilitate maintaining a fluid-tight seal throughout the shelf-life and usage of the dispenser **10**. The bladder **12** (including the integral valve member **58**) may be made of an elastomeric material that is relatively soft in comparison to the vial **12** and valve seat **54**. For example, the bladder **12** may be made of a polymeric material, such as the material sold under the trademark Kraton™, or a vulcanized rubber or other polymeric material. However, as may be recognized by those of ordinary skill in the pertinent art based on the teachings herein, these materials are only exemplary, and numerous other materials that are currently, or later become known for performing the functions of the bladder and/or valve member equally may be used.

As shown in FIG. **1**, when the dispenser is empty, the bladder **14** is fully expanded into engagement with the interior surfaces of the vial **12** such that the variable volume storage chamber **16** is at substantially zero volume. As described in the above-mentioned co-pending patent appli-

cation, the bladder **14** may be formed such that it naturally tends to flex outwardly and create a positive pressure gradient on the fluid or other substance in the storage chamber **16**. Also, in this position, the valve member **58** of the filling valve **56** is in the normally closed position to maintain the interior of the dispenser hermetically sealed. In this condition, the empty dispenser may be sterilized prior to filling, such as by applying gamma, e-beam, or another type of radiation thereto. Then, the sealed, empty and sterilized dispenser may be transported to a sterile filling machine or other filling station without risk of contaminating the sterilized interior portions of the dispenser, as described further below.

Turning to FIG. **3**, the dispenser **10** is filled in a sterile filling machine comprising a sterile enclosure (not shown) of a type known to those of ordinary skill in the pertinent art that includes a laminar flow source **72** for directing a substantially laminar flow of sterilized air or other gas(es) **73** over the dispenser **10** during filling to maintain aseptic conditions. The sterile filling machine further includes an evacuating/filling member **74** that is connected in fluid communication with a vacuum source **76** for drawing a vacuum through the filling member and, in turn, evacuating the interior of the dispenser. As indicated by the arrows in FIG. **3**, the filling member **74** is movable axially into and out of the fill tube **50** of the dispenser to open the filling valve **56** and evacuate the interior of the dispenser. In this mode, and as shown in FIGS. **3** and **4**, the tip **78** of the filling member **74** depresses the flexible valve member **58** only about one-half its full extent of axial mobility. As can be seen best in FIG. **4**, in this position the sealing surfaces **66** and **68** of the valve member **58** are spaced away from their corresponding valve seats **54** and **70**, respectively, to thereby define valve openings therebetween. The vacuum source **76** is actuated to draw air or other gases out of the interior chambers to evacuate the dispenser. After a vacuum is created inside the dispenser, the filling member **74** is moved out of the fill tube **50**, and the spring **60** drives the valve member **58** into the closed position (i.e., the spring **60** urges the sealing surface **66** into engagement with the corresponding valve seat **54**). The sealed, evacuated dispenser then may be sterilized, such as by applying gamma, e-beam or other radiation thereto.

The sterilized, sealed, evacuated dispensers then may be filled with a fluid or other substance, such as a medicament. As indicated in FIGS. **5**A through **5**D, the sterile filling machine further includes a fluid source **80** containing a fluid or other substance to be introduced into the storage chamber of the dispenser, such as a medicament (shown in FIG. **5**A only) coupled in fluid communication with a filling member **74**. The filling member **74** may be the same as the filling member described above, or may be a different filling member. For example, as described further below, the sterile filling machine may include more than one evacuating/filling member, such as a bank of evacuating/filling members, for evacuating a plurality of dispensers, and more than one filling member, such as a bank of filling members, for filling a plurality of dispensers with a fluid or other substance.

In order to fill the dispenser **10** with a fluid or other substance from the fluid source **80**, the tip **78** of the filling member is moved axially inwardly against the valve member **58** of the filling valve **56** to open the valve. As shown in the embodiment of FIG. **5**D, the valve member **58** is moved axially inwardly until the second sealing surface **68** of the valve member sealingly engages the corresponding valve seat **70** to form a fluid-tight seal therebetween. Then, as also shown in FIG. **5**D, fluid is introduced from the fluid source **80**, through the open filling valve **56** and into the storage chamber **16**. The base **62** of the bladder **14** defines one or more grooves **81** or like fluid passageways formed between the base of the bladder **14** and vial **12**, and extending in fluid communication between the inlet aperture **64** of the filling valve and storage chamber **16**. In the fully open position, the second sealing surface **68** and corresponding valve seat **70** prevent fluid from flowing into the piston, and thus prevent such fluid from flowing into the valve **18** during the filling process. As shown in FIGS. **5**B and **5**C, as the fluid is filled into the storage chamber **16**, the bladder **14** collapses and the variable volume chamber **16** correspondingly expands. As shown in FIG. **5**C, in the filled position, the bladder **14** is collapsed toward, or in contact with, the fill tube **50**. Once the storage chamber is filled, the filling member **74** is moved out of the fill tube **50** and the spring **60** of the filling valve **56** closes the valve member **58** to hermetically seal the fluid or other substance within the dispenser. As shown in FIG. **6**A, upon withdrawing the filling member **74** and closure of the filling valve **56**, the fluid or other substance within the storage chamber **16** is drawn into the formerly evacuated space of the piston conduit **36**. As a result, the pump **20** will require at most minimal priming prior to dispensing the first dose of fluid or other substance therefrom.

In sum, and as shown typically in FIGS. **7**A through **7**D, the sealed, empty, sterilized dispensers **10** are introduced into the filling machine. Alternatively, if desired, the sealed, empty dispensers may be sterilized within the filling machine, such as by applying gamma and/or e-beam radiation thereto in a first stage of the sterile filling machine. As shown in FIG. **7**B, the dispensers are first evacuated in a vacuum station. Then, as shown in FIG. **7**C, the sealed, evacuated dispensers are filled in a filling station (both the vacuum and filling stations may include laminar flow to maintain aseptic conditions, as described above). If deemed necessary or desirable, an e-beam or other radiation source may be used to sterilize the exposed surface of the valve member **58** to further ensure sterilization of this surface prior to engagement of the surface with the evacuating/filling member. For example, as described further below, the evacuating and/or filling stations may be located within an e-beam chamber. Alternatively, a laser or other radiation source may be employed to scan or otherwise subject the exposed surface of the valve member **58** to radiation prior to passage through the evacuation and/or filling stations to further ensure the sterility of such surfaces. As shown in FIG. **7**D, the Intact™ filled, sterilized, and hermetically sealed dispensers are discharged from the sterile filling machine and ready for usage.

With reference to FIG. **7**E, in one embodiment, the dispensers are filled in a sterile filling assembly including a sterile enclosure **84** and one or more laminar flow sources **72** (not shown in FIG. **7**E) for providing a substantially laminar flow of filtered/sterilized air over the dispensers during the filling and/or transporting thereof. In some embodiments, the sterile filling assembly is adapted to fill dispensers for containing medicaments, such as ophthalmic or other pharmaceutical or OTC products. However, as may be recognized by those of ordinary skill in the pertinent art based on the teachings herein, the sterile filling assembly equally may be used for filling any of numerous other substances, such as cosmetics and food products. The sterile filling assembly comprises an infeed unit **86** for holding the dispensers to be delivered into the enclosure **84** of the sterile filling assembly. In the illustrated embodiment, the infeed unit **86** is in the form of a rotary table that holds a plurality of dispensers, and

delivers the dispensers at a predetermined rate into the sterile filling assembly. As may be recognized by those of ordinary skill in the pertinent art based on the teachings herein, the infeed unit may take the form of any of numerous devices that are currently known, or later become known for performing the functions of the infeed unit **86**, such as any of numerous different types of vibratory feed drives, or "pick and place" robotic systems.

Prior to installing the dispensers on the infeed unit **86**, the sealed empty dispensers may be sterilized, such as by exposing the containers to gamma radiation, in a manner known to those of ordinary skill in the pertinent art. In addition, the sealed, empty dispensers may be enclosed, sterilized, and transported to the sterile filling assembly in accordance with the teachings of U.S. Pat. No. 5,186,772, entitled "Method of Transferring Articles, Transfer Pocket And Enclosure", and U.S. patent application Ser. No. 10/421,249, entitled "Transfer Port and Method for Transferring Sterile Items", each of which is assigned to the assignee of the present invention and is hereby expressly incorporated by reference as part of the present disclosure.

Once loaded into the sterile filling assembly, the dispensers may be sterilized again (or alternatively, sterilized for the first time) by transmitting radiation from a radiation source **88** onto the sealed, empty dispensers in order to further ensure absolute sterility of the requisite surfaces prior to filling. The radiation may take the form of any of numerous different types of radiation that are currently or later become known for performing this function, such as gamma, e-beam and/or laser radiation.

A conveyor **90** is coupled to the infeed unit **86** for receiving the dispensers delivered by the infeed unit and for transporting the dispensers at a predetermined rate through the sterile filling assembly. In the illustrated embodiment, the conveyor **90** transports the dispensers in a single file relative to each other. The conveyor **90** may take the form of any of numerous different types of conveyers that are currently, or later become known, for performing the functions of the conveyor described herein. For example, the conveyor may take the form of a vibratory feed drive, or may take the form of an endless conveyor belt, or a plurality of star wheels, including, for example, a plurality of receptacles, such as cleats, for receiving or otherwise holding the dispensers at predetermined positions on the conveyor. The conveyor is drivingly connected to a motor or other suitable drive source (not shown), which is controlled by a computer or other control unit (not shown) to start, stop, control the speed, and otherwise coordinate operation of the conveyor with the other components of the sterile filling assembly.

In one embodiment, the radiation source **88** includes at least one e-beam source mounted within an e-beam housing **87** containing therein a filling station **77** including a bank or plurality of filling members **74**. The e-beam source **88** may be any of numerous different types of e-beam sources that are currently, or later become known, for performing the function of the e-beam source described herein. E-beam radiation is a form of ionizing energy that is generally characterized by its low penetration and high dose rates. The electrons alter various chemical and molecular bonds upon contact with an exposed product, including the reproductive cells of microorganisms, and therefore e-beam radiation is particularly suitable for sterilizing dispensers or other containers for medicaments or other sterile substances. As indicated by the arrows in FIG. **7**E, the e-beam source **88** produces an electron beam **89** that is formed by a concentrated, highly charged stream of electrons generated by the acceleration and conversion of electricity. The electron beam **89** may be focused onto the surfaces of the dispensers that will contact or be located in close proximity to the filling members **74** and onto the surfaces of the filling members **74**. In addition, reflective surfaces (not shown) may be mounted adjacent to the conveyor in a manner known to those of ordinary skill in the pertinent art in order to reflect the e-beam, and/or the reflected and scattered electrons of the e-beam, onto the surfaces of interest of the dispensers and/or filling members to ensure adequate sterility of same. Alternatively, or in combination with such reflective surfaces, more than one e-beam source may be employed, wherein each e-beam source is focused onto a respective surface or surface portion of the dispensers and/or filling members to ensure sterilization of each surface area of interest.

The e-beam housing is constructed in a manner known to those of ordinary skill in the pertinent art to define an e-beam chamber and means for preventing leakage of the electrons out of the chamber in accordance with applicable safety standards. In one embodiment, the conveyor **90** defines an approximately U-shaped path within the e-beam chamber **87**, wherein the first leg of the U defines an inlet section and the portion of the chamber onto which the e-beam is directed. However, as may be recognized by those of ordinary skill in the pertinent art based on the teachings herein, the e-beam may be directed throughout the chamber and/or to other portions of the chamber. The current, scan width, position and energy of the e-beam **89**, the speed of the conveyor **90**, and/or the orientation and position of any reflective surfaces, may be selected to achieve at least a 3 log reduction, and in some embodiments about a 6 log reduction in bio-burden testing on the requisite surfaces of the dispensers and/or filling members. In addition, as an added measure of caution, one or more of the foregoing variables also can be selected to achieve at least a 3 log reduction on the sides or other non-contact surfaces of the dispensers and non-contact surfaces of the filling members. These specific levels of sterility are only exemplary, however, and the sterility levels may be set as desired or otherwise required to validate a particular product under, for example, United States FDA or applicable European standards, such as the applicable Sterility Assurance Levels ("SAL").

The sterile filling assembly **84** also may include means for visually inspecting the filling station **77**. This means may take the form of a beta-barrier window (i.e., a window that blocks any e-beam radiation but permits visual inspection therethrough), and/or a CCD, video or other camera mounted within the housing for transmitting to an external monitor images of the filling station. As may be recognized by those skilled in the pertinent art based on the teachings herein, these particular devices are only exemplary, and any of numerous other devices that are currently known, or later become known, for performing the function of permitting visual inspection equally may be employed.

The filling station **77** is located on the opposite leg, or outlet side of the U-shaped conveyor path within the e-beam chamber. In one embodiment, the filling station **77** includes a plurality of filling members **74** mounted over the conveyor **90**, wherein each filling member is drivingly mounted over the conveyor in the same manner as described above. The same filling member may be used to evacuate and to fill the dispensers, or the station may include separate banks of filling members for first evacuating and then filling the dispensers. In this configuration, the filling members used to evacuate the dispensers may be located on the inlet leg of the chamber, and the filling members used to fill the dispensers may be located on the outlet leg of the chamber. Accordingly, each filling member **74** is movable into and out of

engagement with the valve members **58** of the dispensers received within the filling station to evacuate and/or fill the dispensers with a medicament or other substance to be contained therein, and to then withdraw the filling member upon filling the dispensers. In one embodiment, the filling station includes a bank of six filling members **74** mounted in line with each other and overlying the conveyor **90** to allow the simultaneous in-line evacuation and then filling of six dispensers. The filling members **74** may be mounted to a common drive unit (not shown), or each filling member may be individually actuatable into and out of engagement with the valve members of the dispensers. As may be recognized by those of ordinary skill in the pertinent art based on the teachings herein, the filling station may include any desired number of filling members, or may be mounted or driven in any of numerous different ways that are currently known, or later become known, for performing the functions of the filling station described herein. Similarly, the sterile filling assembly may include a plurality of filling stations mounted within the same e-beam chamber, or a plurality of e-beam and filling assemblies, in order to increase or otherwise adjust the overall throughput of the sterile filling assembly. In certain embodiments, the e-beam housing **87** defines a port or other removable passageway (not shown) to allow access to and/or repair and replacement of the filling station **77**.

As described above, the e-beam and filling station is configured so that the filling members **74** are mounted within the e-beam chamber **87**. As a result, the free electrons within the e-beam chamber will impinge upon the filling members. This, in combination with operation of the e-beam **89** which sterilizes the air throughout the e-beam chamber **87**, functions to sterilize the filling members and/or maintain the sterility of the filling members throughout the filling process. Accordingly, since the containers or other dispensers are evacuated and filled within the e-beam chamber **87**, there is virtually no risk that the dispensers will become contaminated between e-beam sterilization and filling. If desired, the air within the e-beam chamber may be ionized to promote multiplication of the free electrons and further enhance the sterility of the filling station **77**. Furthermore, this feature obviates any need for an isolator, as found in many prior art sterile filling machines.

The e-beam source **88** and other applicable components of the e-beam chamber, conveyor systems, and filling assembly may be the same or similar to that disclosed in the following co-pending patent applications which are assigned to the Assignee of the present invention and hereby incorporated by reference as part of the present disclosure: U.S. application Ser. No. 10/600,525, entitled "Sterile Filling Machine Having Needle Filling Station Within E-Beam Chamber"; U.S. Provisional Application No. 60/518,267, filed Nov. 7, 2003, entitled "Needle Filling and Laser Sealing Station"; and U.S. Provisional Application No. 60/518,685, filed Nov. 10, 2003, entitled "Needle Filling and Laser Sealing Station".

As shown in FIG. **7**E, the sterile filling assembly may include one or more additional stations **79** located downstream of the filling station **77**. The additional stations **79** may include a vision system of a type known to those of ordinary skill in the pertinent art for inspecting each valve seal, a level detection system for detecting the level of fluid or other substance within each dispenser to ensure that it is filled to the correct level, and a labeling station. In addition, as shown in FIG. **7**E, the sterile filling assembly may include a rejection unit **81** for pulling off of the conveyer any dispensers that are defective as detected, for example, by the level detection inspection, or due to mislabeling or defective labeling. Then, the acceptable dispensers are removed by a discharge unit **83** for discharging the dispensers into a collection unit **85** for packing and shipping. The rejection and discharge units may take the forms of star wheels, pick and place robots, or any of numerous other devices that are currently or later become known for performing the functions of these units described herein.

A significant advantage of the certain embodiments is that they enable true sterile filling and not only aseptic filling. Yet another advantage of certain embodiments is that the medicament or other substance is filled after subjecting the dispensers to gamma and direct e-beam radiation, thus preventing the radiation from degrading the medicament or other substance to be contained within the dispenser.

Yet another advantage of certain embodiments of the dispensers is that they may hold multiple doses of fluids or other substances, such as medicaments. A further advantage of various dispensers is that the fluids may be preservative free.

In FIG. **8**, another dispenser is indicated generally by the reference numeral **110**. The dispenser **110** is similar to the dispenser **10** described above with reference to FIGS. **1-7**, and therefore like reference numeral preceded by the numeral **1** are used to indicate like elements. A primary difference of the dispenser **110** in comparison to the dispenser **10** is in the construction of the filling valve **156**. As shown in FIG. **8**, the free end of the fill tube **150** defines an axially-extending valve seat **154**, and the base portion **162** of the flexible bladder **114** defines a flexible valve cover **158** that overlies the valve seat **154** to thereby define an annular, axially-extending seam **155** therebetween. In some embodiments, the flexible valve cover **158** and valve seat **154** form an interference fit to thereby maintain a fluid-tight seal when the valve is in the normally closed position. The fill tube **150** defines an annular recess **163** that fixedly receives therein a corresponding annular lobe formed by the base portion **162** of the bladder. The flexible valve cover **158** may define a substantially tapered, or progressively reduced wall thickness when moving axially in the direction of the inlet to the valve toward the interior of the dispenser. This configuration requires progressively less energy to open each respective annular portion of the valve when moving axially from the inlet to the valve to the interior of the dispenser. As a result, once the base of the valve is opened, the pressure is sufficient to cause the respective axial segments of the valve cover **158** to progressively open and then close after passage of fluid therethrough when moving in the axial direction. In certain embodiments, a substantially annular segment of the valve cover **158** substantially always engages the valve seat **154** to maintain the fluid-tight seal across the valve **156** and thereby prevent ingress through the valve of germs, bacteria or other substances. The tip of the fill tube **150** defines an annular flange **184** that is seated in a corresponding recess formed in the base of the vial body **112**, and a tip **186** that is received within the piston **132** to define the piston fluid conduit **136** therebetween.

As shown in FIGS. **9**A and **9**B, the dispenser **110** is filled by slidably receiving a probe **174** within the fill tube **150** such that the tip **178** of the probe is located adjacent to the inlet to the filling valve **156**. As shown in FIGS. **9**B and **9**C, a fixture **188** is movable into engagement with the dispensing valve **118** to evacuate the interior of the dispenser and otherwise to secure the dispenser in the filling station. The fixture **188** includes a housing **190** coupled in fluid communication with a vacuum source **176**, and drivingly connected to a drive unit **192** for moving the fixture into and out

of engagement with the dispensing nozzle **118** of the respective dispenser **110**. The fixture **188** further includes at least two rotating members **194** angularly spaced relative to each other and engageable with the flexible valve cover **124** of the dispensing nozzle. As indicated by the arrows in FIG. **9**C, the rotating members **194** are rotatably driven when placed in contact with the flexible valve cover **124** of the respective dispensing nozzle **118** to compress or pinch a portion of the valve cover located between the rotating members and, in turn, form an opening between the valve cover **124** and respective valve seat **122** coupled in fluid communication with the dosage chamber **138** and interior of the dispenser. The vacuum source **176** is coupled in fluid communication through the fixture housing **190** to the opening formed by the rotating members **194** to, in turn, evacuate the interior of the dispenser through the opening. Once the interior of the dispenser is evacuated, the rotating members **194** are rotated in the opposite direction and/or are released to allow the flexible valve cover to return to its normally-closed position to hermetically seal the evacuated dispenser.

As indicated by the arrow in FIG. **9**C, after evacuating the dispenser and returning the dispensing valve to its closed position, fluid is introduced through the probe **174**, through the seam **155** of the filling valve **156**, through the passageway(s) **181**, and into the storage chamber **116**. The fluid is introduced through the probe **174** at a pressure greater than the valve opening pressure of the filling valve **156** to open the valve and allow the fluid to flow therethrough. As shown in FIG. **9**C, as the storage chamber **116** is filled with fluid, the bladder **114** correspondingly collapses to allow the variable volume chamber **116** to correspondingly expand and receive the fluid. As shown in FIG. **9**D, once the storage chamber **116** is filled with fluid, the probe **174** is released, and the flexible valve cover **158** seals against the valve seat **154** to hermetically seal the fluid within the dispenser. If desired, the filling steps illustrated in FIGS. **9**A through **9**C may be performed within an e-beam chamber as described above in connection with FIG. **7**E.

In FIGS. **10** and **11**, another dispenser is indicated generally by the reference numeral **210**. The dispenser **210** is similar to the dispenser **10** described above with reference to FIGS. **1-7**, and therefore like reference numerals preceded by the numeral **2** are used to indicate like elements. A primary difference of the dispenser **210** in comparison to the dispenser **10** is in the construction of the filling valve **256** and flexible bladder **214**.

As shown in FIGS. **10** and **11**, the flexible bladder **214** defines in its expanded condition an exterior axially-extending cylindrical wall **215**, an interior axially-extending cylindrical wall **217**, and a curvilinear base portion **219** extending between the interior and exterior cylindrical walls. The free end of the fill tube **250** defines an axially-extending valve seat **254**, and the base portion **262** of the inner wall **217** of the flexible bladder **214** defines a flexible valve cover **258** that overlies the valve seat **254** to thereby define an annular, axially-extending seam **255** therebetween. In some embodiments, the flexible valve cover **258** and valve seat **254** form an interference fit to thereby maintain a fluid-tight seal when the valve is in the normally closed position. The fill tube **250** defines an annular recess **263** that fixedly receives therein a corresponding annular lobe formed by the base portion **262** of the bladder. Annular flanges **265** extend outwardly from the fill tube **250** on either side of the annular recess **263**, and are received within corresponding annular recesses formed in the base portion **262** of the inner wall of the bladder to fixedly secure the bladder and valve cover to the fill tube.

The flexible valve cover **258** may define a substantially tapered or progressively reduced wall thickness when moving axially in the direction of the inlet to the valve toward the interior of the dispenser. This configuration requires progressively less energy to open each respective annular portion of the valve when moving axially from the inlet to the valve to the interior of the dispenser. As a result, once the base of the valve **256** is opened, the pressure is sufficient to cause the respective axial segments of the valve cover **258** to progressively open and then close after passage of fluid therethrough when moving in the axial direction. In some embodiments a substantially annular segment of the valve cover **258** substantially always engages the valve seat **254** to maintain the fluid-tight seal across the valve **256** and thereby prevent ingress through the valve of germs, bacteria or other substances.

The dispenser **210** is filled by initially evacuating the dispenser as described above, and then slidably receiving a probe (not shown) within the fill tube **250** such that the tip of the probe is located adjacent to the inlet to the filling valve **256**. Then, fluid is introduced through the probe, through the seam **255** of the filling valve **256**, and into the storage chamber **216**. The fluid is introduced through the probe at a pressure greater than the valve opening pressure of the filling valve **256** to open the valve and allow the fluid to flow therethrough. As the storage chamber **216** is filled with fluid, the exterior wall **215** of the bladder **214** correspondingly collapses toward the interior wall **217** to allow the variable volume chamber **216** to correspondingly expand and receive the fluid. Once the storage chamber **216** is filled with fluid, the probe is released, and the flexible valve cover **258** seals against the valve seat **254** to hermetically seal the fluid within the dispenser.

A significant advantage of the illustrated embodiments is that the dispensers may hold multiple doses of substances and store the substance remaining within the dispenser in a hermetically sealed, sterile condition between doses. Accordingly, in one embodiment, the substance shown is a non-preserved product. Because the variable-volume storage chamber maintains the substance in a sterile, hermetically sealed condition, from the first to the last dose, the use of preservatives may be avoided.

As may be recognized by those of ordinary skill in the pertinent art based on the teachings herein, numerous changes and modifications may be made to the above-described and other embodiments without departing from the spirit of the invention as defined in the claims. For example, the components of the dispensers may be made of any of numerous different materials that are currently or later become known for performing the functions of such components. Similarly, the components of the dispensers may take any of numerous different shapes and/or configurations. Also, the dispensers may be used to dispense any of numerous different types of fluids or other substances for any of numerous different applications, including, for example, ophthalmic, nasal, dermatological, or other pharmaceutical or OTC applications. Further, the sterile filling machine used to fill the dispensers of the present invention may take any of numerous different configurations that are currently, or later become known for filling the dispensers in accordance with the teachings of the present invention. Such sterile filling machines may vary significantly from the filling machine disclosed herein. For example, the filling machines may have any of numerous different mechanisms for sterilizing, feeding, evacuating and/or filling the dispensers. Further, as indicated above, the same filling members or probes may be equipped to both evacuate the dispensers and

fill the dispensers in the same station. Further, the filling valve need not be formed through the bladder, but may extend through the vial body or otherwise may be coupled in fluid communication with the storage chamber to evacuate and/or fill the storage chamber. Alternatively, the dispenser may include one valve for evacuating the interior of the dispenser and another valve for filling the storage chamber of the dispenser. Similarly, the pump and/or dispensing valve each may take a configuration that is different than that disclosed herein. In addition, the variable-volume storage chamber may not be formed by a flexible bladder, but rather may be formed by a piston slidably received within the vial body, as described, for example, in the above-mentioned co-pending patent application. Accordingly, this detailed description of embodiments is to be taken in an illustrative, as opposed to a limiting sense.

What is claimed is:

1. An apparatus comprising:

a body;

a sterile chamber within the body hermetically sealed from the ambient atmosphere;

and

a valve coupled in fluid communication with the chamber and defining (1) a normally closed, fluid-tight position hermetically sealing the chamber from the ambient atmosphere, and (2) an open position allowing the passage of substance through the valve, to one or more of pass substance therethrough from the chamber, or pass substance therethrough to the chamber,

wherein the valve includes a valve member movable between the closed and open positions and defining at least one exposed surface exposed to ambient atmosphere in the closed position;

wherein the valve is configured for engagement with a probe or filling or evacuation member to move the valve member between the closed and open positions so that, when the valve is in the open position, substance passes through the valve without contacting the at least one exposed surface; and

wherein the apparatus is configured to maintain sterility of a sterile substance entering the apparatus and passing through the valve in the open position to the chamber, thereby permitting aseptic passage of sterile substance into the chamber.

2. An apparatus as defined in claim **1**, wherein the valve includes a spring that biases or urges the valve toward the closed position.

3. An apparatus as defined in claim **2**, wherein the spring is formed integral with the valve.

4. An apparatus as defined in claim **3**, wherein the spring is approximately dome-shaped.

5. An apparatus as defined in claim **1**, wherein the spring applies both radially directed and axially directed forces to the valve to bias or urge the valve toward the closed position.

6. An apparatus as defined in claim **1**, wherein at least one flow aperture is formed through the spring and is coupled in fluid communication between the valve and the chamber.

7. An apparatus as defined in claim **1**, further comprising a spring coupled to the valve member and biasing the valve member toward the closed position.

8. An apparatus as defined in claim **7**, wherein the spring is formed integral with the valve member.

9. An apparatus as defined in claim **8**, wherein the spring defines an annular, curvilinear wall extending axially and radially from the valve member.

10. An apparatus as defined in claim **9**, wherein the annular, curvilinear wall of the spring is approximately dome shaped.

11. An apparatus as defined in claim **1**, wherein the valve further includes a valve seat engagable with the valve member in the closed position to form a fluid-tight seal therebetween.

12. An apparatus as defined in claim **1**, wherein the valve includes a valve seat and a sealing surface movable relative to the valve seat between closed and open positions, wherein the sealing surface is engagable with the valve seat in the closed position to form a fluid-tight seal therebetween, and is spaced away from the valve seat in the open position to form a valve opening for the passage of substance therethrough.

13. An apparatus as defined in claim **1**, further comprising a tube coupled in fluid communication with the valve.

14. An apparatus as defined in claim **1**, further including a nozzle in fluid communication with the chamber.

15. An apparatus as defined in claim **1**, further comprising a probe engagable with the valve to thereby open the valve and at least one of pass substance therethrough from the chamber, and pass substance therethrough to the chamber.

16. An apparatus as defined in claim **15**, wherein the probe defines a passageway therethrough and an opening at an end thereof in fluid communication with the passageway configured for passing substance through the valve.

17. An apparatus as defined in claim **15**, further comprising a substance source coupled in fluid communication with the probe for passing substance therethrough.

18. An apparatus as defined in claim **17**, wherein the substance source comprises one or more of medicament, a cosmetic, food product, sterile substance or preservative free substance.

19. A method comprising:

passing a sterile substance into or out of a device comprising a body, a sterile chamber within the body hermetically sealed from the ambient atmosphere, a valve coupled in fluid communication with the chamber and defining (1) a normally closed, fluid-tight position hermetically sealing the chamber from the ambient atmosphere, and (2) an open position allowing the passage of substance through the valve to one or more of pass substance therethrough from the chamber or pass substance therethrough to the chamber, wherein the valve (i) includes a valve member movable between the closed and open positions and defines at least one exposed surface exposed to ambient atmosphere in the closed position; and (ii) is configured for engagement with a probe or filling or evacuation member to move the valve member between the closed and open positions so that, when the valve is in the open position, substance passes through the valve without contacting the at least one exposed surface;

said passing step including:

moving the valve member from the closed position to the open position;

passing the sterile substance through the valve and into or out of the chamber without contacting the at least one exposed surface;

and maintaining the sterility of the sterile substance during the passing step.

20. A method as defined in claim **19**, further comprising biasing the valve toward the closed position.

21. A method as defined in claim **20**, wherein said biasing step includes biasing the valve toward the closed position with a spring having at least one flow aperture therethrough

coupled in fluid communication between the valve and the chamber, and said step of passing substance through the valve includes passing substance through the at least one flow aperture.

22. A method as defined in claim **19**, wherein the valve includes a valve seat and the valve member engagable with the valve seat to define the closed position and movable between the closed and the open position in which the valve member is spaced away from the valve seat, and said moving step includes moving the valve member from the closed position to the open position.

23. A method as defined in claim **19**, further comprising passing substance out of the chamber through a nozzle of the device.

24. A method as defined in claim **19**, further comprising engaging the valve with a probe, wherein said moving step includes moving the valve from the closed position to the open position with an end of the probe.

25. A method as defined in claim **24**, further comprising introducing substance to the chamber from a substance source coupled in fluid communication with the probe.

26. An apparatus comprising:

a body;

a sterile chamber within the body hermetically sealed from the ambient atmosphere;

a first valve coupleable in fluid communication with the chamber and defining (1) a normally closed, fluid-tight position hermetically sealing the chamber from the ambient atmosphere, and (2) an open position allowing the passage of substance through the first valve to one or more of pass substance therethrough from the chamber or pass substance therethrough to the chamber; and

a second valve coupleable in fluid communication with one or more of the first valve or the chamber and defining (1) a normally closed, fluid-tight position preventing the passage of substance therethrough, and (2) an open position for passing substance therethrough;

wherein the apparatus is configured to maintain sterility of a sterile substance entering the apparatus and passing through the first valve in the open position to the chamber, thereby permitting aseptic passage of sterile substance into the chamber.

27. An apparatus as defined in claim **26**, further including a spring that biases the first valve toward the closed position.

28. An apparatus as defined in claim **27**, wherein the spring is integral with the first valve.

29. An apparatus as defined in claim **27**, wherein the spring is approximately dome-shaped.

30. An apparatus as defined in claim **26**, wherein the first valve includes a valve member movable between the closed and open positions and the valve member is biased toward the closed position.

31. An apparatus as defined in claim **30**, wherein the first valve further includes a valve seat engageable with the valve member in the closed position to form a fluid-tight seal therebetween.

32. An apparatus as defined in claim **27**, wherein the spring includes at least one flow aperture therethrough coupled in fluid communication between the first valve and the chamber.

33. An apparatus as defined in claim **26**, wherein the first valve includes at least one valve seat and at least one sealing surface movable relative to the at least one valve seat between closed and open positions, wherein in the closed position the at least one sealing surface engages the at least one valve seat to form a fluid-tight seal therebetween, and in the open position the at least one sealing surface is spaced away from the at least one valve seat to form a valve opening for the passage of substance therethrough.

34. An apparatus as defined in claim **26**, wherein the second valve includes a valve member movable between the closed and open positions and the valve member is biased toward the closed position.

35. An apparatus as defined in claim **26**, further comprising a tube coupled in fluid communication with the first valve.

36. An apparatus as defined in claim **35**, further comprising a substance source coupled in fluid communication with the tube for introducing substance therethrough and into the chamber.

37. An apparatus as defined in claim **36**, wherein the substance source comprises one or more of medicament, a cosmetic, food product, sterile substance or preservative free substance.

38. A method comprising:

passing a sterile substance into and out of a device comprising a body, a sterile chamber within the body hermetically sealed from the ambient atmosphere, a first valve coupleable in fluid communication with the chamber and defining (1) a normally closed, fluid-tight position hermetically sealing the chamber from the ambient atmosphere, and (2) an open position allowing the passage of substance through the first valve to one or more of pass substance therethrough from the chamber or pass substance therethrough to the chamber, and a second valve coupleable in fluid communication with one or more of the first valve or the chamber and defining (1) a normally closed, fluid-tight position preventing the passage of substance therethrough, and (2) an open position for passing substance therethrough, said passing step including:

moving the first valve from the closed position to the open position;

moving the second valve from the closed position to the open position;

passing the sterile substance through the first valve;

passing the sterile substance through the second valve; and

maintaining sterility of the sterile substance entering the device during said passing steps.

39. A method as defined in claim **38**, further including biasing one or more of the first valve or the second valve toward the respective closed position thereof.

40. A method as defined in claim **39**, wherein said biasing step includes biasing the first valve toward the closed position with a spring having at least one flow aperture therethrough coupled in fluid communication between the first valve and the chamber, and said step of passing substance through the first valve includes passing substance through the at least one flow aperture.

41. A method as defined in claim **38**, wherein the first valve includes a valve seat and a valve member engagable with the valve seat to define the closed position and movable between the closed and the open position in which the valve member is spaced away from the valve seat, and said step of moving the first valve from the closed position to the open position includes moving the valve member from the closed position to the open position.

42. A method as defined in claim **38**, further comprising introducing substance to the device from a substance source coupled in fluid communication therewith.

43. An apparatus comprising:

a body;

a sterile chamber within the body hermetically sealed from the ambient atmosphere;

a valve coupled in fluid communication with the chamber and defining (1) a normally closed, fluid-tight position hermetically sealing the chamber from the ambient atmosphere, and (2) an open position allowing the passage of substance through the valve to one or more of pass substance therethrough from the chamber or pass substance therethrough to the chamber, and

a spring formed integral with the valve that biases or urges the valve toward the closed position, wherein the spring one or more of (i) is approximately dome-shaped or (ii) defines an annular, curvilinear wall extending axially and radially from the valve member.

44. An apparatus comprising:

a body;

a sterile chamber within the body hermetically sealed from the ambient atmosphere;

a first valve coupleable in fluid communication with the chamber and defining (1) a normally closed, fluid-tight position hermetically sealing the chamber from the ambient atmosphere, and (2) an open position allowing the passage of substance through the first valve to one or more of pass substance therethrough from the chamber or pass substance therethrough to the chamber;

a spring formed integral with the first valve that biases or urges the first valve toward the closed position, wherein the spring one or more of (i) is approximately dome-shaped or (ii) defines an annular, curvilinear wall extending axially and radially from the valve member; and

a second valve coupleable in fluid communication with one or more of the first valve or the chamber and defining (1) a normally closed, fluid-tight position preventing the passage of substance therethrough, and (2) an open position for passing substance therethrough.

45. An apparatus as defined in claim **1**, further comprising a probe or filling or evacuation member configured to engage the at least one exposed surface, move the valve member between the closed and open positions, and pass substance through the valve without contacting the at least one exposed surface.

46. A method as defined in claim **19**, further comprising engaging a probe or filling or evacuation member with the at least one exposed surface, moving the valve member between the closed and open positions, and passing substance through the valve without contacting the at least one exposed surface.

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